Available online at www.sciencedirect.com

ScienceDirect

Tanta Dental Journal 11 (2014) 75–84

www.elsevier.com/locate/tdj

Platelet rich fibrin versus Hemcon dental dressing following dental extraction in patients under anticoagulant therapy

R.M. Eldibany*

Faculty of Dentistry, Alexandria University, Egypt

Received 1 March 2014; revised 7 April 2014; accepted 21 April 2014
Available online 27 September 2014

Abstract

Objectives: Dental extractions in heart surgery patients treated with artificial mechanical heart valves under anticoagulant oral therapy can be difficult as these patients present a significant risk for postoperative hemorrhagic complications. This study was performed to evaluate the use of Platelet Rich Fibrin (PRF) and Hemcon dental dressing (HDD) in cardiac patients taking Warfarin following dental extraction.
Methods: 20 patients were involved in this study with an age range of 36–62 years. Patients having an International Normalized Ratio (INR) >3.5 were excluded. Extraction was performed under local anesthesia and as atraumatic as possible. Patients were allocated equally in two groups; group A: where PRF was inserted into the extraction socket, while group B: the extraction socket was packed by HDD.
Results: Complete hemostasis was achieved in all cases with no delayed bleeding. Patients in group A showed minimal pain and accelerated healing, while those in group B showed extreme to moderate pain on the first few days following extraction and retarded healing. Four patients developed alveolar osteitis.
Conclusions: PRF has good antihemorrhagic properties and increases tissue healing and wound closure, thus allowing for a quick recovery without significant painful events. HDD has excellent hemostatic properties and can be used safely in such patients but with small amounts.

Keywords: Anticoagulant therapy; Platelet rich fibrin; Chitosan; Hemcon dental dressing; Dental extraction

1. Introduction

Dental extractions in heart surgery patients treated with artificial mechanical heart valves under anticoagulant oral therapy is difficult as these patients present a significant risk for postoperative hemorrhagic complications [1,2]. The most commonly prescribed oral anticoagulants for these patients are warfarin and acetylsalicylic acid. Therapeutic levels of warfarin are

* Oral & Maxillofacial Surgery Department, Alexandria University, Alexandria, Egypt. Tel.: +2 01227391890; fax: +2 034868922.
E-mail address: riham.eldibany@hotmail.com.
Peer review under the responsibility of the Faculty of Dentistry, Tanta University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.tdj.2014.04.002
1687-8574/

measured by the International Normalized Ratio (INR). The British Society of Hematology has published guidelines on anticoagulant control which recommend a maximum target INR of 3.5, with a range of 3–4 [3].

Currently, many authors do not recommend suspending the anticoagulant therapy and replacing it with heparin injection intravenously or deep subcutaneous before a minor surgery to avoid serious thromboembolic complications [4]. To control the hemorrhagic risk in patients under anticoagulant therapy, several protocols have been proposed in the literature. Some authors have recommended a combination of local antifibrinolytic therapy and hemostatic agents for the prevention of postoperative bleeding [5]. Other authors have suggested that many patients can safely undergo outpatient oral surgical procedures without changes in their regular therapeutic anticoagulant regimen and without additional medical interventions, or by using the tranexamic acid as an antifibrinolytic local agent for 2 days after the surgery [6–8]. While other investigators have proposed the sole use of fibrin glue to prevent the hemorrhagic complications, however these fibrin products are expensive and raise the question of the potential for infectious contaminations [9–12].

The development of platelet concentrate technologies offers simplified and optimized production protocols for concentrated platelet-rich plasma (cPRP). Because of legal restrictions on blood handling, a second-generation platelet concentrate, which is neither fibrin glue nor a classical platelet concentrate, was developed in France by Choukroun et al., in 2001 [13]. The preparation of this relatively new biomaterial, called platelet-rich fibrin (PRF) requires neither anticoagulant nor bovine thrombin. PRF is a strictly autologous fibrin matrix containing a large quantity of platelet and leukocyte cytokines and it is widely used to accelerate soft and hard tissue healing. Autologous PRF is considered as a healing biomaterial, which was initially used in oral implantology by its promoters, and presently, studies have shown its application in various disciplines of dentistry [14].

On the other hand, chitosan preparations of various molecular weights, degrees of deacetylation and with further molecular derivatization patterns have attracted much attention because of their potentially beneficial biological properties. These properties include hemostasis, antimicrobial activity, stimulation of healing, tissue engineering scaffolds, and drug delivery [15–22].

The HemCon Dental Dressing (HDD) has been used extensively under the name HemCon Bandage to stop bleeding in combat wounds and other severe trauma. HDD is a compressed chitosan acetate dressing that was developed as a hemostatic agent [23–25]. HDD is chitin, which is manufactured from freeze-dried shrimp shells. It is an insoluble polysaccharide polymer of glucosamine that is purified and partially deacetylated to form soluble chitosan aqueous gel. Chitosan gel is then freeze dried in molds to make a highly electropositive sponge-like material that is hemostatic and adapts well to oral surgical wounds [20,26]. Chitosan has a positive charge and attracts red blood cells (RBC) and platelets, which are negatively charged through ionic interaction; thus, a strong seal is formed at the wound site. [25] This supportive, primary seal allows the body to activate its coagulation pathway effectively, initially forming organized platelets. Therefore, HDDs are designed to maintain this seal and serve as a frontline support structure as the platelets and red blood cells continue to aggregate until hemostasis is achieved [23,27].

Therefore, the purpose of this study was to test the null hypothesis that there will be no difference in the effectiveness of PRF and HDD in wound healing and in the prevention of hemorrhagic complications after dental extractions in patients receiving oral anticoagulant therapy.

2. Materials and methods

This is a randomized clinical trial and was approved by the institutional review board and the ethical committee of the Faculty of Dentistry, Alexandria University, and an informed consent was obtained from all patients before their inclusion in the study.

This study was conducted on 20 patients referred to the Oral and Maxillofacial Surgery department, Faculty of Dentistry, Alexandria University. All patients were cardiac patients and had undergone heart valve replacement and were currently taking Warfarin.[1] They required extraction of a single mandibular posterior tooth. Extractions were performed for all patients without altering the dose of the anticoagulant. Patients who had an INR >3.5 on the day of operation or had a history of liver disease or coagulopathies were excluded from this study. The patients were randomly divided into two groups: group A, where the extraction sockets were packed with PRF, and group B, where the extraction sockets were packed with HDD. The allocation of patients into either group was random non-blind as there was no way to mask the HDD group

[1] Marevan®, Glaxo, Egypt.

Fig. 1. A pre-operative orthopantogram of a patient in group A showing left mandibular third molar indicated for extraction.

from the PRF group where blood was collected from the patient.

A full medical history was taken and an orthopantogram and clinical examination were performed. Antibiotic prophylaxis was given to all patients two days pre-operatively, once a day, in the form of 875 mg Amoxicillin and 125 mg Clavulanic acid.[2] A pre-operative INR was performed for all patients on the day of extraction. If the INR was more than 3.5, the patient was excluded from the study.

Local anesthesia, 2% lidocaine and 1:100,000 epinephrine was given to all patients using the inferior alveolar nerve block technique and long buccal nerve infiltration. Dental extractions were then performed as atraumatic as possible, using extraction forceps and elevators when needed. Immediately following extraction, the sockets were packed with either PRF or HDD.

Group A: (Ten patients)

20 ml of blood were collected without anticoagulant from the brachial vein 12 min before extraction. The blood was transferred and equally divided in two 10 ml sterile glass tube, and was immediately centrifuged using a table centrifuge at 3000 rpm for 12 min. The absence of anticoagulant implies the activation of most platelets in contact with the glass tube walls in a few minutes and the release of the coagulation cascades. Fibrinogen is initially concentrated in the high part of the tube, before the circulating thrombin transforms it into fibrin. A fibrin clot is then obtained in the middle of the tube, just between the red corpuscles at the bottom and acellular plasma at the top. The success of this technique entirely depends on the speed of blood collection and transfer to the centrifuge. Quick handling is the only way to obtain a clinically usable PRF clot. After centrifugation, each PRF clot was separated from the red blood cell base and placed directly into the post-extraction sockets, and stabilized by 3/0 silk suture (Figs. 1—7).

Fig. 2. Left mandibular third molar indicated for extraction.

Group B: (Ten patients)

HemCon® dental dressing[3] (HDD) 10 mm × 12 mm, was placed into the extraction sockets at the height of the alveolar bone. Whenever needed, the dressing was trimmed using a scissors to fit inside the sockets. Direct finger pressure was then applied over the extraction site for 40—60 s after placement of the HDD. No suturing was done according to the manufacturers' recommendations (Figs. 8—12).

The time of hemostasis was recorded for each patient using a stop watch. Antibiotics were continued three days post-extraction in the form of 875 mg amoxicillin and 125 mg clavulanic acid once a day. Analgesics were prescribed every 8 h for 3 days in the form of diclofenac potassium 50 mg.[4] Post-extraction sites were monitored daily for a week to assess potential late hemorrhagic complications and to evaluate pain and tissue healing. Relative pain scores were evaluated using the Visual Analogue Scale (VAS) [28], where 0 means no pain and 10 being the worst pain the patient had ever experienced. Patients were also evaluated for alveolar osteitis. Sutures were removed one week following extraction.

[2] Augmentin™ 1 gm, Egypt.

[3] HemCon medical technologies, Inc., Portland, USA.

[4] Cataflam®, Novartis Pharma Company.

Fig. 3. Glass test tubes showing the 3 layers of the centrifuged blood.

Fig. 5. Placing the PRF clot inside the extraction socket.

3. Results

Twenty patients were involved in this study, 11 males (55%) and 9 females (45%). Their ages ranged between 36 and 62 years (mean 46.65 years). All patients were under anticoagulant therapy using warfarin due to: prosthetic heart valve (10 patients, 50%), rheumatic heat disease (7 patients, 35%), or myocardial infarction (3 patients, 15%). The INR of patients ranged between 1 and 3.5 (mean = 2.28; group A = 2.29 and group B = 2.27) (Table 1 & Chart 1).

Complete hemostasis was achieved in all patients in both groups. Regarding the time of hemostasis, there was insignificant difference between both groups; in group A, the mean time was 47.6 ± 1.3 s, while in group B, the mean time was 51.3 ± 2.1 s. No postoperative bleeding occurred in any patient in either group on the day of extraction or on the following days (Chart 2).

In group A, no cases of alveolitis were reported in any patient, and there was no notable postsurgical pain (VAS average 2, ranging between 1 and 3) on the 2nd post-extraction day and 0 score on the following days. Moreover, a quick healing of the extraction site was already noted 2 days following extraction, and all

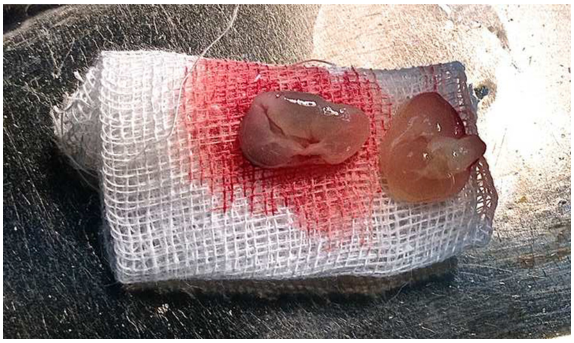

Fig. 4. The PRF clot.

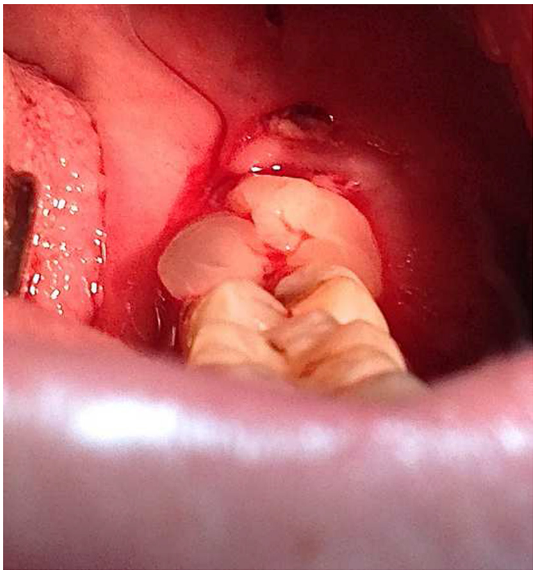

Fig. 6. The PRF clot placed inside the socket.

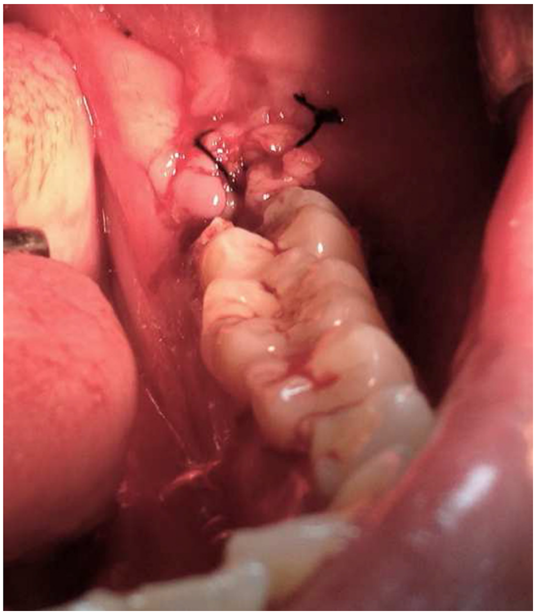

Fig. 7. PRF sutured in place.

alveolar sockets were closed by a proliferating gingival tissue at the time of suture removal one week post-extraction (Fig. 13).

While in group B, four cases reported severe pain (VAS = 8) in the first 48 h following extraction, which was subsided gradually till the 7th post-extraction day, due to the occurrence of alveolar osteitis. In those patients, healing was not complete on the 7th post-operative day and remnants of the HDD were seen in the extraction sites (Fig. 14). Curettage was performed and complete healing was observed on the 2nd post-operative week. Two cases showed post-operative pain of VAS 5 on the first two post-extraction days, then decreased to 3 on the 3rd day and completely disappeared on the 5th post-extraction day, complete healing took place on the 10th post-extraction day. The other four patients in group 2 showed minimal pain and uneventful healing (Chart 2).

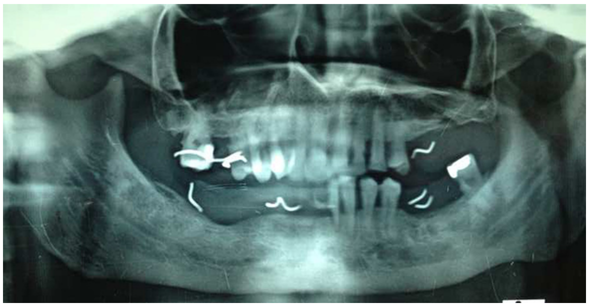

Fig. 8. A pre-operative orthopantogram of group B showing left mandibular third molar indicated for extraction.

Fig. 9. Left mandibular third molar indicated for extraction.

4. Discussion

All patients in this study were treated without altering their anticoagulation medication regimens, based on the evidence that the benefit of preventing thromboembolism outweighs the risk of bleeding. The current consensus recommends avoiding the interruption of anticoagulant therapy and preventing hemorrhagic complications by working with therapeutic INR levels, and adopting local hemostatic measures [29].

In the study published by Sacco et al., in 2007 [30], they revealed that there were no differences between reducing the dose of the oral anticoagulant (OAC) or maintaining the OAC dose with the use of local hemostatic measures in patients undergoing oral surgical procedures.

On the other hand, not all authors agree with this view and there are protocols that recommend interruption or reduction of OAC in the days prior to the intervention to secure subtherapeutic INR levels (INR < 2) in a short period of time before the operation [31,32].

In this study we compared the effectiveness of the PRF and the HDD in those patients. Both the PRF and HDD have shown excellent hemostasis properties on the time of extraction. Patients who were treated with the PRF showed minimal pain and accelerated healing, while those treated with the HDD showed extreme to moderate pain on the first few days post-extraction and

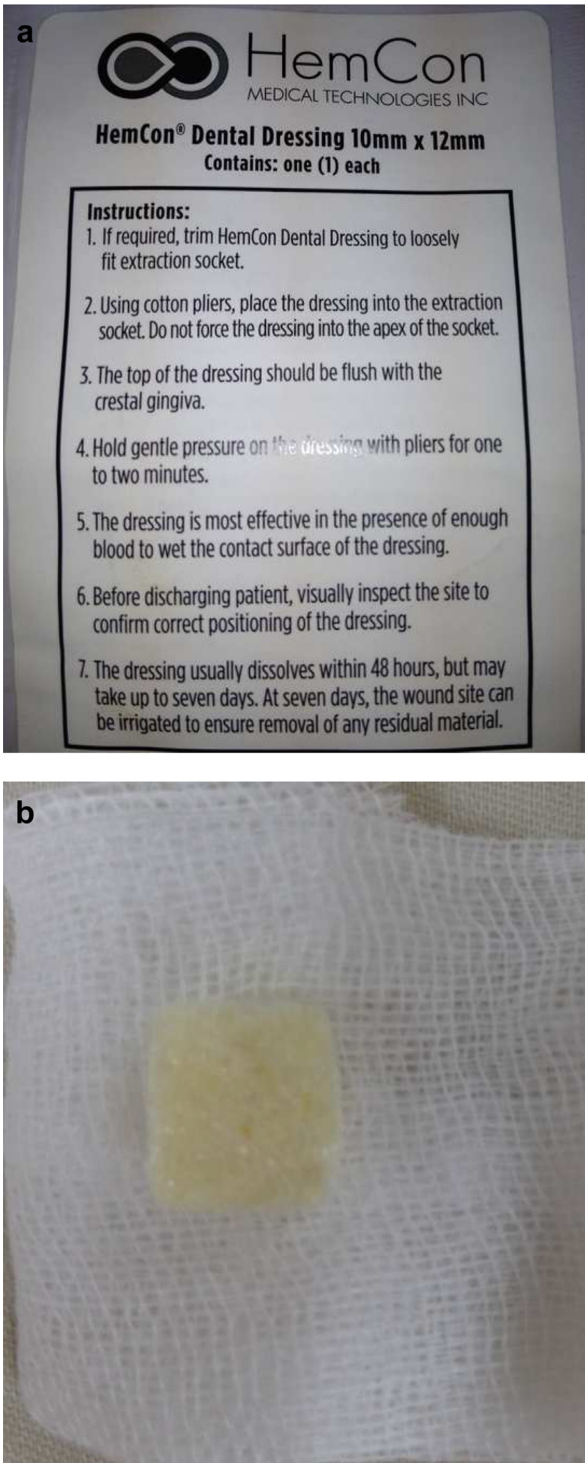

Fig. 10. a, b The Hemcon dental dressing (HDD).

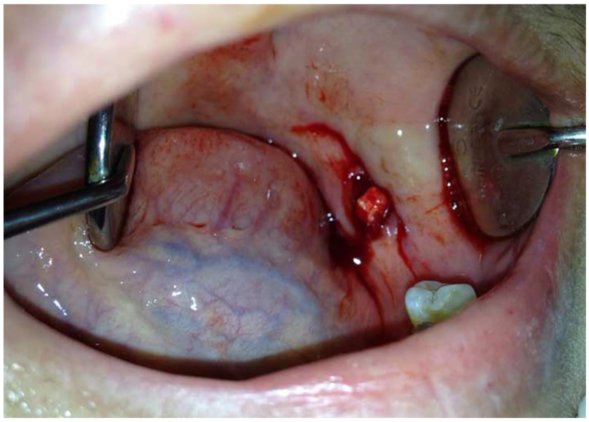

Fig. 11. HDD immediately after insertion in the extraction socket.

retarded healing, in addition to the presence of remnants of HDD in four patients.

During PRF processing by centrifugation, platelets are activated and cytokines are released. Analysis of the PDGF-BB, TGF-β1, and IGF-I within the PRF clot exudate serum, revealed that slow fibrin polymerization during PRF processing leads to the intrinsic incorporation of platelet cytokines and glycanic chains in the fibrin meshes, which allows for their progressive release over time (7–11 days), as the network of fibrin disintegrates. Moreover, during PRF processing, leucocytes could also secrete cytokines in reaction to the hemostatic and inflammatory phenomena artificially induced in the centrifuged tube. This concept also could explain the reduction of postoperative infections when PRF is used as a surgical additive and the clinically observed healing properties of PRF [13,33,34].

Therefore, the slow release of cytokines certainly explains the immediate anti-hemorrhagic properties of the PRF clot. Furthermore, in this study, no delayed bleeding was reported, which is a significant problem in patients under anticoagulant therapy. The slow release of growth factors from the PRF membrane and the strong fibrin architecture of the clot accelerate and improve soft tissue and bone healing. As the wound closure is accelerated, delayed bleedings are logically avoided. Moreover, PRF is rich in leukocytes, and these cells may be a significant asset for protecting the surgical sites against local infections and associated delayed healing [35,36].

These results are in accordance with other studies in literature reporting the effect of PRF in wound healing. Lundquist et al. [37] in 2013 and Jorgensen et al. [38] in 2011 suggested that the L-PRF could be beneficial for the healing of recalcitrant wounds due to the

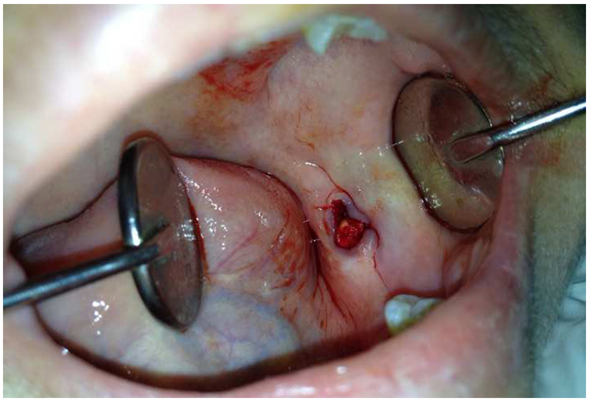

Fig. 12. Hemostasis after 1 min of placing the HDD.

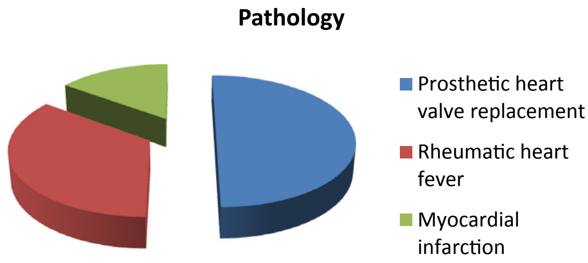

Chart 1. Showing etiology of anticoagulant therapy.

continued release of PDGF-AB over several days. Also, Chignon-Sicard et al. [39] in 2012 investigated the efficacy of L-PRF in a randomized controlled clinical trial of wound healing and demonstrated that a single L-PRF application on fresh postoperative hand wounds showed a median improvement of 5 days in comparison with the standard treatment.

On the other hand, although the HDD sites showed excellent hemostatic properties, we observed initial raised pain scores. Also, four cases showed alveolar osteitis, which may be due to the presence of remnants of the HDD in the sockets, probably due to over packing or deeply packing the material in the extraction sockets in the first few cases, resulting in retarded dissolution of the material.

Hemcon is manufactured from freeze-dried chitosan and molds to form a highly electropositive sponge-like material. This charge facilitates blood clot formation because it allows binding with red blood cells, which are negatively charged, allowing the formation of an extremely viscous clot that seals the wound site and causes hemostasis. In addition, this property attracts other chemotactic factors involved in the clotting process. HDD material requires active bleeding; thus, the more bleeding takes place, the better the HDD material performs which is quite useful during surgical procedures [27,40].

In the study performed by Malmquist et al. [27] in 2008, they also concluded that HDD has proved to be a clinically effective hemostatic agent following oral surgery procedures for all patients, including those patients under anticoagulant therapy. The HDD achieved hemostasis in less than 1 min. On the other hand, they stated that it had an improved surgical wound healing capacity and that the pain scores and the incidence of alveolar osteitis were lower for the HDD treated sites, but they were not significantly different than the control-treated sites, which is contradictory to our results. In their study they used small amounts of the HDD as they found out that if an excessive amount of the material was used or if the extraction socket was fully packed, small amounts of unreacted residual acetic acid in the HDD would cause a minor transient elevation in relative pain scores the first day or two after surgery. This phenomenon may explain the elevated pain scores in this study during the first two days following extraction in the HDD group which subsided once the acetic acid was fully dissolved in oral fluids.

Table 1
Showing sex, age and INR in both groups.

	Group A (mean)	Group B (mean)
Sex	6:4	5:5
Age	45.8 years ± 2.33	47.5 years ± 3.01
INR	2.29 ± 0.98	2.27 ± 0.71

Shen et al. [41] in 2006 observed the enhancing effects of chitosan on platelet adhesion and aggregation, as well as the release of growth factor from human platelets stimulated by chitosan exposure, which may help explain our positive findings regarding hemostasis. In the study performed by Kale et al. [23] in 2012, they stated that the sites that received the HDD had improved postoperative healing with minimal complications when compared to the control site. They attributed their findings to the antibacterial properties of chitosan as it increases the permeability of the inner and outer membranes and ultimately disrupts the bacterial cell membranes, releasing their contents. Thus HDD provides an antibacterial barrier against a wide range of Gram positive and Gram negative organisms [42].

The results of this study could validate the use of PRF during dental extractions for the prevention of postoperative bleeding in patients on anticoagulant therapy. The advantages of PRF are not only related to its anti-hemorrhagic properties; PRF is also a filling

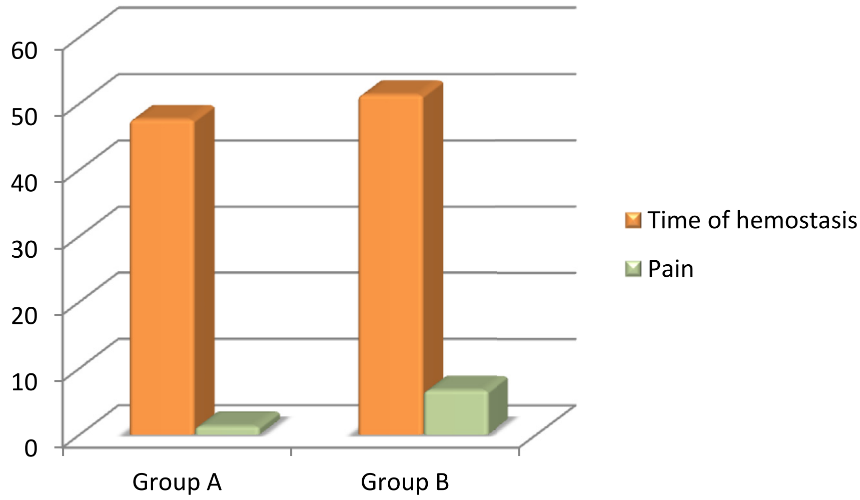

Chart 2. Showing difference in pain and hemostasis levels between both groups.

healing biomaterial and accelerates wound closure. Its immune content may help protect the extraction sockets against unavoidable infections, and by enhancing soft tissue healing, PRF also reduces the duration of the contamination of the surgical site by oral bacteria. With PRF filling, there are no side effects and no significant discomfort nor painful events. However, postoperative pain or discomfort was reported by patients treated with HDD. Foreign materials inserted within fresh extraction sockets always disturb the healing process, whereas PRF, because it is a natural optimized blood clot, is completely tolerated.

Fig. 13. Healed extraction site after one week in group A.

5. Conclusion

The main advantage of PRF is its versatility: PRF has good antihemorrhagic properties and increases tissue healing and wound closure, thus allowing for a quick recovery without significant painful events. Many other applications of these antihemorrhagic and healing properties could be tested and evaluated in patients under anticoagulant therapy.

Fig. 14. Extraction socket one week post-extraction showing remnants of HDD in group B.

The HDD also has excellent hemostatic properties and can be used safely in patients under anticoagulant therapy, but with small amounts and avoid overpacking the extraction sockets.

References

[1] Sammartino G, Dohan Ehrenfest DM, Carile F, Tia M, Bucci P. Prevention of hemorrhagic complications after dental extractions into open heart surgery patients under anticoagulant therapy: the use of leukocyte- and platelet-rich fibrin. J Oral Implantol 2011;37:681–90.

[2] Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94:57–64.

[3] Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugar AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg 2002;40:248–52.

[4] Little JW, Miller CS, Henry RG, McIntosh BA. Antithrombotic agents: implications in dentistry. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:544–51.

[5] Gaspar R, Brenner B, Ardekian L, Peled M, Laufer D. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. Quintessence Int 1997;28:375–9.

[6] Souto JC, Oliver A, Zuazu-Jausoro I, Vives A, Fontcuberta J. Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: a prospective randomized study. J Oral Maxillofac Surg 1996;54:27–32. discussion 323.

[7] Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered? J Oral Maxillofac Surg 2000;58:131–5. discussion 135–6.

[8] Beirne OR. Evidence to continue oral anticoagulant therapy for ambulatory oral surgery. J Oral Maxillofac Surg 2005;63:540–5.

[9] Carter G, Goss A. Tranexamic acid mouthwash—a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int J Oral Maxillofac Surg 2003;32:504–7.

[10] Carter G, Goss A, Lloyd J, Tocchetti R. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. J Oral Maxillofac Surg 2003;61:1432–5.

[11] Rakocz M, Mazar A, Varon D, Spierer S, Blinder D, Martinowitz U. Dental extractions in patients with bleeding disorders. The use of fibrin glue. Oral Surg Oral Med Oral Pathol 1993;75:280–2.

[12] Zanon E, Martinelli F, Bacci C, Zerbinati P, Girolami A. Proposal of a standard approach to dental extraction in haemophilia patients. A case-control study with good results. Haemophilia 2000;6:533–6.

[13] Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:E37–44.

[14] Gupta V, Bains VK, Singh GP, Mathur A, Bains R. Regenerative potential of platelet rich fibrin in dentistry: literature review. AJOHAS 2011;1:22–8.

[15] Dai T, Tegos GP, Burkatovskaya M, Castano AP, Hamblin MR. Chitosan acetate bandage as a topical antimicrobial dressing for infected burns. Antimicrobial Agents Chemother 2009;53:393–400.

[16] Aksungur P, Sungur A, Unal S, Iskit AB, Squier CA, Senel S. Chitosan delivery systems for the treatment of oral mucositis: in vitro and in vivo studies. J Control Release 2004;98:269–79.

[17] Azad AK, Sermsintham N, Chandrkrachang S, Stevens WF. Chitosan membrane as a wound-healing dressing: characterization and clinical application. J Biomed Mater Res B Appl Biomater 2004;69:216–22.

[18] Di Martino A, Sittinger M, Risbud MV. Chitosan: a versatile biopolymer for orthopaedic tissue-engineering. Biomaterials 2005;26:5983–90.

[19] Kheirabadi BS, Acheson EM, Deguzman R, Sondeen JL, Ryan KL, Delgado A, et al. Hemostatic efficacy of two advanced dressings in an aortic hemorrhage model in swine. J Trauma 2005;59:25–34.

[20] Kumar MN, Muzzarelli RA, Muzzarelli C, Sashiwa H, Domb AJ. Chitosan chemistry and pharmaceutical perspectives. Chem Rev 2004;104:6017–84.

[21] Pusateri AE, McCarthy SJ, Gregory KW, Harris RA, Cardenas L, McManus AT, et al. Effect of a chitosan-based hemostatic dressing on blood loss and survival in a model of severe venous hemorrhage and hepatic injury in swine. J Trauma 2003;54:177–82.

[22] Rabea EI, Badawy ME, Stevens CV, Smagghe G, Steurbaut W. Chitosan as antimicrobial agent: applications and mode of action. Biomacromolecules 2003;4:1457–65.

[23] kale TP, Singh AK, Kotrashetti SM, Kapoor A. Effectiveness of Hemcon dental dressing versus conventional method of hemostasis in 40 patients on oral antiplatelet drugs. Sultan Qaboos Univ Med J 2012;12:330–5.

[24] Della Valle A, Sammartino G, Marenzi G, Tia M, Espedito di Lauro A, Ferrari F, et al. Prevention of postoperative bleeding in anticoagulated patients undergoing oral surgery: use of platelet-rich plasma gel. J Oral Maxillofac Surg 2003;61:1275–8.

[25] Wedmore I, McManus JG, Pusateri AE, Holcomb JB. A special report on the chitosan-based hemostatic dressing: experience in current combat operations. J Trauma 2006;60:655–8.

[26] Yang J, Tian F, Wang Z, Wang Q, Zeng YJ, Chen SQ. Effect of chitosan molecular weight and deacetylation degree on hemostasis. J Biomed Mater Res B Appl Biomater 2008;84:131–7.

[27] Malmquist JP, Clemens SC, Oien HJ, Wilson SL. Hemostasis of oral surgery wounds with the HemCon dental dressing. J Oral Maxillofac Surg 2008;66:1177–83.

[28] Campbell WI, Lewis S. Visual analogue measurement of pain. Ulster Med J 1990;59:149–54.

[29] Jiménez Y, Poveda R, Gavaldá C, Margaix M, Sarrión G. An update on the management of anticoagulated patients programmed for dental extractions and surgery. Med Oral Patol Oral Cir Bucal 2008;13:E176–9.

[30] Sacco R, Sacco M, Carpenedo M, Mannucci PM. Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different intensity targets. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:E18–21.

[31] Marietta M, Bertesi M, Simoni L, Pozzi S, Castelli I, Cappi C, et al. A simple and safe nomogram for the management of oral

anticoagulation prior to minor surgery. Clin Lab Haematol 2003;25:127—30.

[32] Russo G, Corso LD, Biasiolo A, Berengo M, Pengo V. Simple and safe method to prepare patients with prosthetic heart valves for surgical dental procedures. Clin Appl Thromb Hemost 2000;6:90—3.

[33] Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part II: platelet-related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e45—50.

[34] Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates? Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e51—5.

[35] Dohan DM, de Peppo GM, Doglioli P, Sammartino G. Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): a gold standard to achieve for all surgical platelet concentrates technologies. Growth Factors 2009;27:63—9.

[36] Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol 2009;27:158—67.

[37] Lundquist R, Holmstrøm K, Clausen C, Jørgensen B, Karlsmark T. Characteristics of an autologous leukocyte and platelet-rich fibrin patch intended for the treatment of recalcitrant wounds. Wound Repair Regen 2013;21:66—76.

[38] Jørgensen B, Karlsmark T, Vogensen H, Haase L, Lundquist R. A pilot study to evaluate the safety and clinical performance of leucopatch, an autologous, additive-free, platelet-rich fibrin for the treatment of recalcitrant chronic wounds. Int J Low Extrem Wounds 2011;10:218—23.

[39] Chignon-Sicard B, Georgiou CA, Fontas E, David S, Dumas P, Ihrai T, et al. Efficacy of leukocyte- and platelet-rich fibrin in wound healing: a randomized controlled clinical trial. Plast Reconstr Surg 2012;130:819e—29e.

[40] Azargoon H, Williams BJ, Solomon ES, Kessler HP, He J, Spears R. Assessment of hemostatic efficacy and osseous wound healing using HemCon dental dressing. J Endod 2011;37:807—11.

[41] Shen EC, Chou TC, Gau CH, Tu HP, Chen YT, Fu E. Releasing growth factors from activated human platelets after chitosan stimulation: a possible biomaterial for platelet-rich plasma preparation. Clin Oral Implants Res 2006;17:572—8.

[42] Burkatovskaya M, Tegos GP, Swietlik E, Demidova TN, P Castano A, Hamblin MR. Use of chitosan bandage to prevent fatal infections developing from highly contaminated wounds in mice. Biomaterials 2006;27:4157—64.